Lumpy Skin Disease

Disease Monograph Series – 23

Virus | Capripoxvirus | Poxviridae| Cattle

IDRC | Bartay

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Acronyms

AU	African Union
AU-IBAR	African Union Inter-African Bureau for Animal Resources
BBRSC	Biotechnology and Biological Sciences Research Council
BMGF	Bill and Melinda Gates Foundation
CaPV	Capripox virus
CVO	Chief Veterinary Officer
DIVA	Differentiate infected from vaccinated animals
DVS	Director Veterinary Services
ELISA	Enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
IAEA	International Atomic Energy Agency of the United Nations
IFAT	Indirect fluorescent antibody test
IM	Intramuscular
KS-1	Kenyan sheep pox vaccine strain
KSGV	Kenyan sheep and goat pox virus
LSD	Lumpy skin disease
LSDV	Lumpy skin disease virus
NGO	Non-governmental organization

OIE	World Animal Health Organization
PCR	Polymerase chain reaction
SGP	Sheep and goat pox
SHF	Small holder farmer
TPP	Target Product Profile
WHO	World Health Organization of the United Nations

Executive Summary

Etiology and relevance

Lumpy skin disease (LSD), a viral disease of cattle, was first described in Zambia in 1929, and is now endemic in most part of Africa. Characterised by significant morbidity although the mortality rate is generally low, losses occur from decreased milk production, abortion, infertility, loss of condition and damaged hides. The economic impact of LSD on livestock production in Africa is so high that the disease has been selected as one of 14 diseases impacting negatively on poor livestock keepers on the continent, with annual losses estimated at USD 487 million. Lumpy skin disease virus (LSDV) is a capripoxvirus, of the genus Capripoxvirus, in the family Poxviridae. LSDV is closely related antigenically to sheep and goat poxviruses. Although these three viruses are distinct, they cannot be differentiated with routine serological tests.

A double-stranded DNA virus, LSDV, like other poxviridae, has a large size, an attribute that has been extensively exploited to use this virus as vector for expressing foreign viral genes and generating recombinant multivalent vaccines. Another potentially beneficial attribute of the LSDV is its remarkable stability and ability to survive for long periods at ambient temperature, especially in dried forms. The virus is also is very resistant to inactivation.

Epidemiology and transmission

LSD is a disease of cattle, with *Bos taurus* bieng more susceptible to clinical disease than *Bos indicus*. The role of wild fauna is still not clear. Some animals, such as the giraffe and impala are highly susceptible to experimental infection and suspected clinical disease has been described in certain type of wild animals; antibodies have also been found in African buffalo, greater kudu, waterbuck, reedbuck, impala, springbok, and giraffe. Following inoculation LSDV replicates in sheep and goats.

The primary method of transmission is mechanical by arthropod vector. Though no specific vector has been identified to date, mosquitoes (e.g. *Culex mirificens* and *Aedes natrionus*) and flies (e.g. *Stomoxys calcitrans and Biomyia fasciata*) are believed to play a major role in transmission of the virus. Other possible and minor source of transmission could be direct contact, and ingestion of feed and water contaminated with infected saliva.

From being restricted to Sub-Saharan Africa where it has been endemic, LSD is currently occurring on almost the entire African continent, has spread to the Middle East and entered Europe where it is currently present in Turkey and Greece. It has also been reported in the northern Caucasus region of Russia, Dagestan and Chechnya. LSD is feared now to have the potential to become established in other parts of the world.

With an incubation period in the field believed to be from 2 to 5 weeks, the clinical signs of LSD range from inapparent to severe. Host susceptibility, dose and route of virus inoculation affect the severity of disease. Following a period of fever, the nodules on the skin start appearing within two days and are the most

characteristic sign of LSD. The nodules expand also to mucous membranes and internal organs. Enlarged lymph nodes, edema of the skin, and sometimes death follow. Secondary bacterial infections are common within the necrotic cores. Decreased feed intake in affected cattle would result in milk yield dropping markedly, and animals becoming emaciated. Pregnant animals may abort. Permanent or temporary infertility may occur in bulls due to subsequent orchitis and testicular atrophy. An important point for trade is the fact that the virus can be excreted in the semen for prolonged periods.

Immunity to LSD is predominantly cell mediated and requires a replicating agent to be effectively stimulated. In infected animals, the virus spread from cell to cell, thus is out of reach of circulating antibodies. Subsequently circulating antibodies can only limit the spread of the virus in experimental animals, but do not prevent replication of the virus at the site of infection. Furthermore, the immune status of a previously infected or vaccinated animal cannot be related to serum levels of neutralising antibodies.

Diagnostics

Clinically a presumptive diagnosis of the disease can be made based on highly characteristic clinical signs of LSD, although mild and asymptomatic disease may be difficult to diagnose and rapid laboratory methods are needed to confirm the diagnosis.

It is always important to differentiate LSD from other skin pseudo LSD (bovine herpesvirus-2, BHV-2), insect bites, Demodex infection, onchocerciasis, besnoitiosis and dermatophilosis.

At laboratory level the identification of the agent relies mainly on genome detection through PCR, electron microscopy of biopsy or crusts, and virus isolation. There is also the antigen ELISA that has been described. Serological tests include virus/serum neutralisation (golden standard test for serology), indirect fluorescent antibody test, capripox antibody ELISA and seldom Western Blot. Most serological tests however would not differentiate between different capripox.

Control

There is no specific treatment for LSD though strong antibiotic therapy may avoid secondary bacterial infections. Free countries are urged often to restrict import of livestock, carcasses, hides, skins and semen from infected countries or regions with ongoing enzootic situation. Sanitary prophylactic measures in infected countries or during outbreaks are often not effective. Vaccination is the most widely and effective control strategy.

Vaccination and vaccination strategies

Only live attenuated vaccines are currently commercially available for LSD. They are either homologous LSDV or heterologous based on attenuated SGP strains. The attenuated Neething strain, the first LSD vaccine strain to be developed (in South Africa) is widely used on cattle in Africa, with the Kenya sheep and goat pox (KSGP or KS-

1) used for both LSD and SGP. Other SGP vaccine strains exist and are also used in some regions for LSD. However it is known that the cross-protection is not satisfactory and the use of these vaccines has been restricted to those countries where sheep and goat pox are endemic. The Neethling and KSGP based vaccines are produced by several African vaccine manufacturing laboratories. In recent years several Middle East countries have also been producing vaccine based essentially on SGP strains.

Even though the development of improved LSD vaccines has not been a major priority by many research groups or countries, capripox have been considered over the past two decades as ideal recombinant vaccine vectors due to their size and stability, thus good to express foreign genes. Recombinant LSD or KS-1 expressing PPR, rinderpest or rabies genes have been assessed, although no such commercial vaccine exist to date.

Increased interest and concern on the effectiveness of the LSD vaccines have been raised over the past few years due to the spread of LSD into more countries in Asia and Europe, and to the lack of protection observed in countries such as Ethiopia with the locally produced vaccine. Several studies have been conducted and more are ongoing to assess the suitability of the different vaccines used for the control of LSD. In parallel, research on new generation LSD vaccines is looking into 4 options, namely (1) the use of LSD as a vector for expression of foreign genes and generation of multivalent vaccines; (2) the generation of attenuated vaccines by knocking out virulent genes but maintaining the immunogenicity; (3) the development of DIVA vaccines by knocking out non-essential but immunogenic genes and (4) the development of non-replicating vaccines (inactivated vaccines).

The future of LSD vaccines and vaccination

The new interest on LSD due to the risk the disease is posing for Europe is directing vaccine research toward solutions for preventing the introduction of the disease, rather than the control in endemic regions. There is a drive to ensure the availability of LSD vaccines that prevent infection and spread of the wildtype virus, and also have DIVA characteristics. Some of these characteristics, such as DIVA, may not be relevant for endemic regions. In most of these regions, where the disease has been causing serious economic losses, the main challenge is the availability of the vaccine and the lack of clear vaccination programs and strategies.

It seems also very critical that the vaccines used in endemic regions be produced for virus seed materials properly evaluated, including at molecular level to confirm their identity, especially for the main homologous vaccine in use, the Neethling strain, but also produced under required quality standards and protocols. The availability and inclusion of such vaccine in well validated control program is a matter of priority, more than product characteristics such as DIVA.

Clinical disease overview

Etiology

Lumpy skin disease (LSD, also called Pseudo-urticaria, Neethling virus disease, exanthema nodularis bovis, and knopvelsiekte) is an infectious disease of cattle. It is caused by a virus (LSDV) from the family Poxviridae which is divided into two subfamilies— poxviruses affecting insects (Entomopoxvirinae) and vertebrates (Chordopoxvirinae)—and several genera. The genus Capripoxvirus (CaPV) comprises LSDV, sheep pox virus (SPV) and goat pox virus (GPV). Although the disease was first seen in Zambia in 1929, the prototype of LSDV, Neethling strain, was isolated in South Africa [5][11].

Poxviruses are large (320–260 nm), they can be enveloped or non-enveloped, brick- or oval-shaped viruses with similar morphology (except certain members of the group such as the parapoxviruses) [5]. LSDV is a double-stranded DNA virus, with a 151 kbp genome consisting of a central coding region with identical 2.4-kbp inverted terminal repeats and 156 putative genes. The genes encoding host range, virulence and immune evasions are located at the terminal parts of the genome [4]. It has been shown by DNA analysis using restriction endonucleases on field samples and vaccine strains that there is 80 % homology between strains of capripoxviruses [7]. The genomes of SPV and GPV are very similar to that of LSDV, sharing 96 % nucleotide identity within the genus [4][7]. It is not possible to distinguish between different strains of CaPV using serological assays [12]. Molecular studies have demonstrated that LSDV, SPV and GPV are phylogenetically distinct [4][7] and, recently, by sequencing the host-specific G-protein-coupled chemokine receptor (GPCR), or RNA polymerase genes, species-specific molecular assays have been developed for differentiation of CaPVs, enabling the phylogenetic grouping of CaPVs [4]

LSDV is known to be remarkably stable; surviving for long periods at ambient temperature, especially in dried forms, and is very resistant to inactivation: it can be recovered from skin nodules kept at –80C°C for 10 years and infected tissue culture fluid stored at 4°C for 6 months. The virus can survive in necrotic skin nodules for up to 33 days or longer, desiccated crusts for up to 35 days and at least 18 days in air-dried hides [5][7]. It can remain viable for long periods in the environment. Meanwhile, the virus is susceptible to sunlight and detergents containing lipid solvents, while, in dark environmental conditions, such as contaminated animal sheds, it can persist for many months [11].

Epidemiology

Susceptible animal species

- LSD is a disease of cattle (*Bos taurus*, zebus, domestic Asian buffalo). *Bos taurus* is more susceptible to clinical disease than *Bos indicus.*
- Natural infections in Asian water buffalo (*Bubalus bubalis*) have been reported in Egypt, but with significantly lower prevalence rate (1.6 %) than in cattle (30.8 %) [11][12].
- Lumpy skin disease virus replicates in cell cultures of sheep and goat origin. In experimentally infected sheep and goats there is local reaction at the inoculation site, but there are no reports on clinical disease in small ruminants caused by LSDV.
- Clinical signs of LSD have been demonstrated in impala (*Aepyceros melampus*) and giraffe (*Giraffa camelopardalis*) after experimental inoculation with LSDV. LSD was reported in an Arabian oryx (*Oryx leucoryx*) in Saudi Arabia [11].
- Antibodies against capripoxes have been detected in blue wildebeest (*Connochaetes taurinus*), black wildebeest (*Connochaetes gnu*), springbok, eland (*Taurotragus oryx*) and impala. The seroprevalence varied from 10 to 27 %, averaging 17 % in a grassland and 33 % in a forest transition environment (Barnard, 1997). Antibodies were also detected in serum samples collected from African buffalo (*Syncerus caffer*) in Kenya [5][11]. In another study, low levels of antibodies were detected in kudu (*Tragelaphus strepsiceros*), two waterbuck species (*Kobus ellipsiprymnus* and *Kobus defassa*), reedbuck (*Redunca arundinum*), impala, springbok and giraffe, leading to the conclusion that the samples may have contained non-specific virus inhibitors. However, the antibody titres in the giraffe and reedbuck samples were as high as in convalescent cattle that were assumed to be indicative of past infection [5][11].

Distribution

LSD has traditionally been restricted to sub-Saharan Africa but over the past 15 years has spread to most African countries, the Middle East and some European countries. The outbreaks outside Africa started with those in the Middle East between 2006 and 2007, and in Mauritius in 2008. Between 2012 and 2013 the disease spread in Northern Israel and Libanon. Between 2013 and 2015 it spread further: was first reported in Turkey, and in 2015, the first incursion of LSDV was reported in the European Union territory in Greece, close to the river Evros and the Turkish border. It has since been reported in the northern Caucasus region of Russia, Dagestan and Chechnya [13]. See Figure 1.

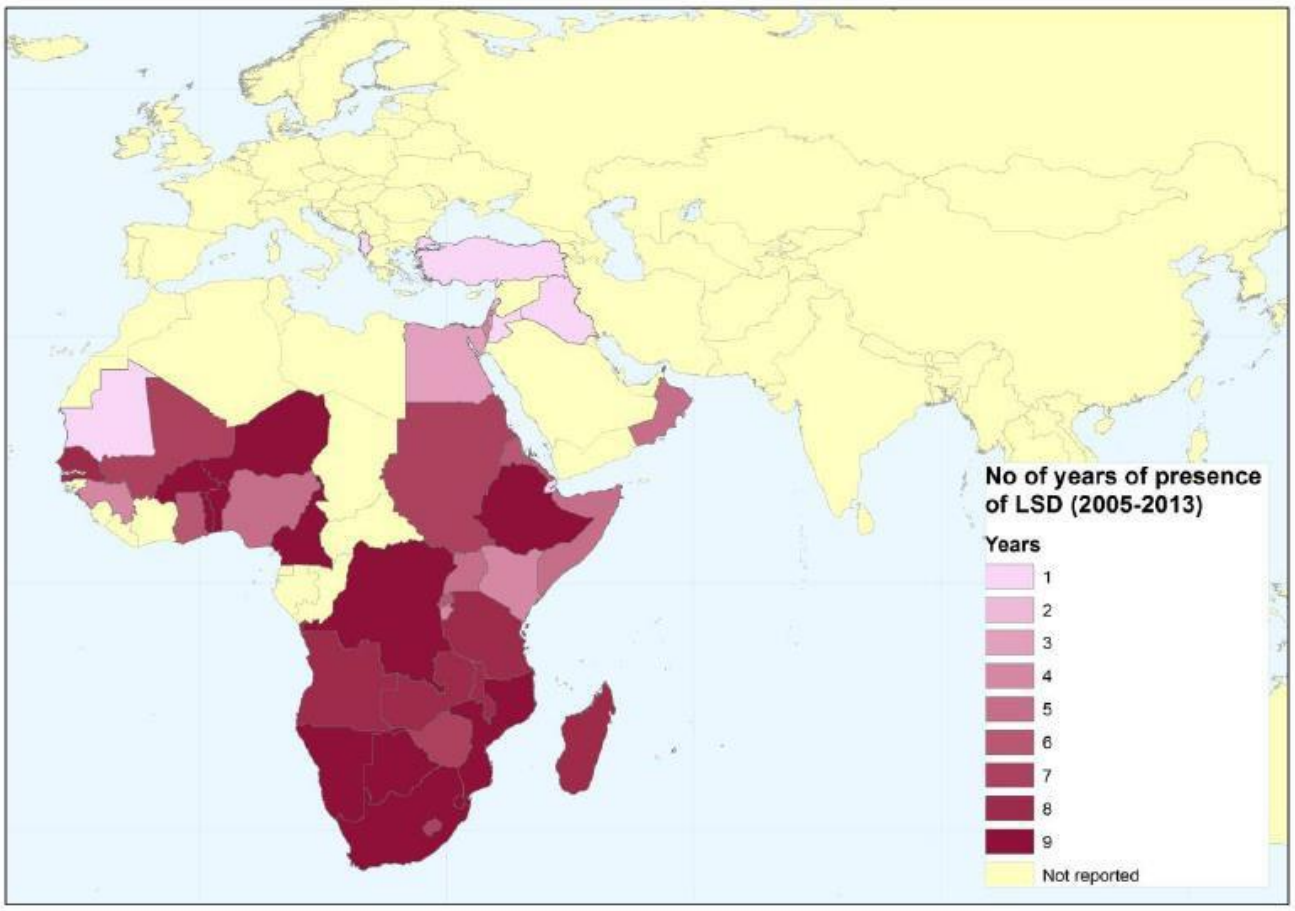

Figure 1: Map showing number of years of presence of LSD in different countries as reported to OIE for the period 2005–2013 (EU).

Transmission

It is currently believed that the main mode of transmission of LSDV is mechanical via blood-feeding insects with frequent feeding habits [11]. The most important vector is likely to vary between affected regions, depending on the climate, season, environmental temperature, humidity and vegetation, favouring different insect and tick species. The relative importance of vectors may also vary within a region as changes in climate may affect the local arthropod populations and viral spread [7].

The virus has been recovered from *Stomoxys spp.* and *Musca confiscate* although attempts at transmitting the infection with these flies were unsuccessful [12]. Other indirect evidence that a vector(s) is involved in the transmission of LSD is the failure of control measures, such as quarantine, to stop its spread both in South Africa and Kenya [5].

The virus seems inefficiently transmissible directly between animals. Transmission through semen has been demonstrated experimentally. Transmission may also occur by ingestion of feed and water contaminated with infected saliva [7][11]

Recent data have shown molecular evidence of transstadial and transovarial transmission of LSDV by *Rhipicephalus decoloratus* ticks, and mechanical or intrastadial transmission by *R. appendiculatus* and *Amblyomma hebraeum* ticks [1].

Immunity to LSD

Serological studies with cattle vaccinated with sheep and goat poxvirus have shown that many animals resist challenge with virulent LSDV when they have no detectable fluorescent or neutralising antibody to the virus. Most animals do show a serological response after field infections. As is the case for most pox viruses, immunity to LSD is considered to be predominantly cell mediated and the immune status of animals does not directly correspond to serum neutralizing antibody titers [7].

With the exception of enveloped forms of the viruses, which are released into the blood, most progeny LSDV remain inside infected cells. By spreading from cell to cell, the virus is out of reach of circulating antibodies. Circulating antibodies against capripox virus are able to limit the spread of the virus in experimental animals, but do not prevent replication of the virus at the site of infection [1][7]. The immune status of a previously infected or vaccinated animal cannot be related to serum levels of neutralising antibodies.

All capripoxes share a common major antigen for neutralising antibodies; animals recovered from infection by one virus are believed to be at least partially protected from infection with the other. It is not possible to distinguish CaPVs with the serum neutralisation test (SNT), fluorescent antibody test (FAT), indirect fluorescent antibody test (IFAT) or agar gel immunodiffusion (AGID) [11][12]

Animals that recover from apparent or inapparent natural infection with LSD develop antibodies capable of neutralising up to 3 logs of the virus and are also resistant to reinfection, whereas those that have been vaccinated or showed mild disease develop low levels of neutralising antibodies [7].

Clinical Signs

The severity of clinical signs varies widely ranging from very mild to severe. *Bos taurus* cattle are more susceptible than *Bos indicus* (zebu) and lactating cows and fine-skinned dairy breeds, such as the Guernsey and Jersey, are particularly susceptible [5][11]

In acutely affected animals the first symptoms are fever followed by development of swellings or nodules in the skin that give the disease its name (Figure 2). These nodules are 2-5 cm across and occur in particular on the

head, neck, udder and perineum. The nodules, which can number many hundreds, are painful, affecting the skin, subcutaneous tissue and sometimes the underlying muscle and can become necroctic causing deep cratered scars. Other symptoms include a marked reduction in milk yield, depression, anaemia, excessive salivation and ocular and nasal discharge. Pox lesions are also present in the mouth, nose, testicles and bladder. The superficial lymph nodes, draining areas of affected skin, are significantly enlarged and the limbs can become swollen causing the animals to be reluctant to move. Secondary bacterial infections are common affecting the teats, tendons and joints and fly strike can occur at the site of the skin lesions. Abortions can occur and the aborted foetuses have sometimes been reported to also be covered in nodules. Affected bulls and cows can become temporarily or permanently sterile [5][11].

Figure 2: Lumpy skin disease in cattle. [12]

Recovery from LSD is slow, essentially due to emaciation, pneumonia, mastitis, and necrotic skin plugs, which are subject to fly strike and shed leaving deep holes in the hide: it can take as long as 6 months [5][11]. Mortality rates vary: some reports suggest average rates of 1-3% in zebu and around 10% in dairy breeds. In an epizootic of LSD that occurred between 1981 and 1986 in Tanzania, Kenya, Zimbabwe, Somalia and the Cameroon, mortality rates of 20% of affected cattle were reported. Deaths are probably largely due to secondary bacterial infections [5][6][11].

Pathology

Nodules are characteristics and involve all layers of skin, subcutaneous tissue, and often adjacent musculature, with congestion, haemorrhage, oedema, vasculitis and necrosis. Lymph nodes draining affected areas are enlarged, accompanied with lymphoid proliferation, oedema, congestion and haemorrhage. Pox lesions are observed on mucous membrane of the mouth, the pharynx, epiglottis, tongue and throughout the digestive tract [5][11]

Diagnosis

Clinical Diagnosis

Though field incubation period is not much described, in experimental infection, following inoculation the onset of fever is in 6–9 days, and first skin lesions appear at the inoculation site in 4–20 days [11]. LSD should be suspected when the characteristic skin nodules, fever and enlarged superficial lymph nodes are seen. Painful nodules of 2–5 cm in diameter develop over the entire body, particularly on the head, neck, udder and perineum between 7 and 19 days after virus inoculation.

Differential Diagnosis

Although severe LSD is highly characteristic, milder forms can be confused with diseases including pseudo-lumpy skin disease/ bovine herpes mammillitis (Bovine Herpesvirus 2), dermatophilosis, ringworm, insect or tick bites, besnoitiosis, ringworm, Hypoderma bovis infestation, photosensitization, bovine papular stomatitis (Parapoxvirus), urticaria and cutaneous tuberculosis. Most of these diseases can be distinguished from lumpy skin disease by the clinical signs, including the duration of the disease, as well as histopathology and other laboratory tests [11][12]

Laboratory diagnosis

- Confirmation of LSD in a new area requires virus isolation and identification. Samples for virus isolation and antigen-detection ELISA should be taken during the first week of signs, before neutralising antibodies have developed. Samples for PCR can be collected after this time [15]. In live animals, biopsy samples of skin nodules or lymph nodes can be used for PCR, virus isolation and antigen detection. Scabs, nodular fluid and skin scrapings may also be collected. In early, viraemic stages of the disease, blood samples can be collected for virus isolation

- The identification of LSDV can be achieved through:
    - *PCR*: on EDTA blood, semen, biopsy, or tissue culture samples. While the general capripox real-time PCR method is highly sensitive and specific, differentiation with other capripoxes may require sequencing and phylogenetic analysis [11][15]
    - *Transmission electron microscopy*: on biopsy material or desiccated crusts
    - *Capripox antigen detection ELISA*: on biopsy suspension or tissue culture fluid
- Serological tests
    - Virus neutralisation – cross reacts with all capripoxviruses
    - Indirect fluorescent antibody test: cross reaction with parapoxviruses
    - Capripox antibody ELISA.
    - Western blot: highly sensitive and specific but expensive and is difficult to perform; it requires purified antigens, and cannot be used as a primary assay but can be used if inconclusive or positive SNT/ELISA results need to be confirmed [7][11][15]
- Other tests described but not widely used are:
    - LSD penside test [7]
    - Loop-mediated isothermal amplification assays (LAMP), which have been published but are not yet ready for pen-side use [7]

Incidence and Prevalence in Selected Countries

Global

Incidence data by country

Data of outbreaks reported to the World Animal Health Organization (OIE) are shown in Tables 1 and 2. Data are not always reliable, as many countries doesn't seem to report, or to be reporting consistently over time.
http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail

Similar information but presented in a different manner can be seen in Annex 1.

Table 1: Number of LSD outbreaks reported to the OIE between 2005-2015 (Numbers given only for the target countries). Source: OIE.
http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
West Africa											
Burkina Faso	13	17	81	13	9	195	82	21	8	52	3
Ivory Coast	>1	0	+	+	+	+	+	+	1	-	
Mali	2	5	>2	0	0	2	0	1	0	1	0
Senegal	3	5	1	190	2	2	1	+	0	5	+
East Africa											
Ethiopia	27	72	129	130	284	180	177	179	230	166	34
Kenya	+	0	9	0	0	0	0	3	9	24	9

Rwanda	-	0	>4	12	>6	>4	+	51	54	-	-
Tanzania	138	41	99	19	12	12	10	10	25	37	7
Uganda	7	?	?	?	?	?	+	2	3	>8	-
Southern Africa											
Madagascar	>52	16	26	+	+	36	7	6	13	6	4
Malawi	>9	>12	26	>5	>3	5	1	24	34	-	-
Mozambique	>4	>6	18	7	3	2	>4	1	0	0	-
South Africa	17	156	229	153	54	56	213	92	56	127	18
Zambia	-	50	52	103	123	108	+	74	141	90	-

- No information, + Present but quantitative data not known, ? Disease suspected

2- AU-IBAR: The number of outbreaks reported to AU-IBAR is included in the Pan African Animal Resources Year Book. **(http://www.au-ibar.org/pan-african-animal-resources-yearbook?showall=&limitstart=)** and can be seen for the countries of interest in Table 2 below.

Table 2: Number of LSD outbreaks reported to the AU-IBAR from 2005 to 2015 (numbers given only for the target countries). Source: AU-IBAR Year Books.

Country	2005*	2006**	2007	2008	2009	2010	2011	2012	2013	2014	2015
West Africa											
Burkina Faso			53		7	195	82	20	8	52	
Ivory Coast											
Mali				11		2	1	1		1	
Senegal				190	3	1	1	2	26	4	
East Africa											

Ethiopia			275	420	1	341	187	197	337	131	
Kenya			51		5	53 cases	12	20	5	19	
Rwanda						14			14		
Tanzania			128	207 cases	87 cases	56 cases	11	9	26	30	
Uganda			11	7	6	11	63	9	3		
Southern Africa											
Madagascar			131	1614 cases	505 cases	227 cases	43				
Malawi			23		3	2		21	38	2	
Mozambique			38		4	8	2		1	1	
South Africa			216	149	8	36	146	96	59	122	
Zambia			54	11	37	39	37	33	111	80	

*AU-IBAR didn't start yet producing data for LSD
**No individual country report available; 7 countries reported to a total of 334 outbreaks

Regional

Prevalence data by country

No data or recent data on prevalence has been found for any of the focus countries, except for Ethiopia and South Africa.

Ethiopia

Year	Area	Species of animal	No. samples tested	% positive	Reference
2012-2013	West Wollega, Oromiya	Indigenous crossbred cattle	554 samples from 252 herds	Individual: 6.43 Herd: 5.959 See details in Figure below.	**Abera et al, 2015**
2011-2012	Four districts of Afar and Tigray	Questionnaires to herd owners	393	Herd: 44 Individual: 7.4	**Hailu et al, 2014**
2012	15 Districts	Cattle	2368	IFAT and VNT Herd: Midland agro-climate zone: 64 Highland: 26 Lowland: 50 Individual: Midland agro-climate zone: 31 Highland: 24 Lowland: 23	**Gari et al, 2012**
2011	Adama	Traded Borena Bulls	11,189	6.1	Alemayehu et al, 2012
2010	15 Districts	Questionnaires to herd owners	330	Herd Total: 42.8 Midland agro-climate	Gari et al, 2010

				zone: 55.2 Lowland: 22.3 Highland: 43.5 Individual: 8.1	

PAs in both districts	No of sampled	No of Sero Positive (%)
Were Seyo	63	0 (0)
BikiltuTokuma[a]	58	1 (1.72)
Jogir	46	0 (0)
Chutta Kaki	44	3 (6.81)
LelisaYesus	61	8 (13.11)
Horda Daleti	48	1 (2.12)
Nebo Daleti	57	5 (8.77)
Werebabo Siben	52	3 (5.77)
Haroji Serdo	55	5 (9.1)
Dongoro Dissi	60	9 (15)
Ground Total	544	35 (6.43)

Figure 3: LSD seroprevalence by district in West Wollega. Source: Abera et al, 2015 PA: Peasant Associations

South Africa

Year	Area	Species of animal	No. samples tested	% positive	Reference
2014	Kruger National Park and Hluhluwe-iMfolozi Park	Buffalo	KNP: 138 HiP: 110	iELISA: 28.2 SNT: 7.6	**Fagbo et al, 2014**

Economic and Social Impacts at Global and Regional Levels, and in Selected Countries

LSD impacts on cattle production and on a number of aspects:

- Cattle are particularly susceptible to LSD during peak lactation, which together with secondary mastitis and prolonged high fever, affects milk production.
- Abortions and temporary or permanent infertility occur among infected animals.
- Emaciation and a long convalescence period can significantly decrease the growth rate in beef cattle.
- More importantly, deep pox lesions in the skin leave permanent scars, decreasing the value of skins and hides for use in the leather industry [13]

In a study by Gari et al. [8] conducted in dairy cattle in the in the highlands of the Oromia region, located near Addis Ababa, it was reported that the average duration of the lactation period of local zebu cows was shorter (240 days) than for Holstein Friesian/cross breeds (305 days) and for zebu cattle the milk take-off per lactation was significantly lower (323 l) than for Holstein Friesian/cross cows (3694 l). In this study comprising a selection of farms, the Holstein Friesian and Jersey breeds were found to be almost three times more susceptible for LSDV than zebus (annual cumulative incidence of LSDV infection of 33.93% and 13.41% respectively) and the annual mortality rates due to LSDV infection of zebus was considerably lower than for Holstein Friesian (1.26% compared to 7.43%). In addition, estimated total production losses in infected cattle due to decrease in milk and beef production, loss of draft power, mortality, veterinary treatments and vaccination costs were estimated to be 6.43 USD per head for local zebu and 58 USD per head for Holstein Friesian/cross breeds.

In South Africa LSD has become one of the major causes of economic losses to non-commercial communal cattle owners [10]

As part of their disease prioritization effort, the Bill and Melinda Gates Foundation identified LSD as one of 14 diseases that negatively impact on poor livestock keepers. The total annual losses to small farmers in Africa due to LSD were calculated to be USD 487 million [16].

Disease Prevention and Control Methods

Treatment (Control)

There is no treatment for Lumpy Skin Disease although antibiotic therapy may prevent severe secondary infections developing [15].

Prophylaxis (Prevention)

In theory, control of the disease can be achieved by implementation of strict quarantine and effective movement controls, slaughter of infected and in-contact animals, proper disposal of carcases, disinfection of affected premises and vector control [11]. The outbreak in Israel in 1989 was rapidly eliminated by a combination of these methods together with vaccination [7]. In Africa, however, lack of capacity in the veterinary services and the difficulties of enforcing quarantine and movement restrictions in remote areas means that this approach has proven to be generally ineffective. Important to note that no country in sub-Saharan Africa, however, has succeeded in eradicating LSD once it has occurred [7]

As biting flies are most probably the most important method of transmission of the disease, control by quarantine and movement control is generally not very effective. In endemic areas control is therefore essentially confined to vaccination [5].

When LSD appears in a new area, non-enzootic, it is recommended that all infected and contact cattle be slaughtered immediately and the carcasses destroyed in an attempt to eliminate the focus of infection. A vaccination cover with a 25 to 50 km radius may then be established around the focus and all cattle movements stopped within that zone. Alternatively, it might be decided to leave all cattle in the zone unvaccinated, allowing the manifestation of any- residual infection [6]

When an outbreak occurs in an enzootic area and LSD has already spread extensively, slaughter policies- are inappropriate and extensive vaccination campaigns are recommended. The imposition of strict movement controls are suggested because, although these do not contain outbreaks of LSD, they do prevent new foci from

becoming established at a certain distance. Vaccination will greatly reduce the morbidity and economic effects of an epizootic but may not completely limit the extension of-LSD. Follow-up vaccination of calves and re-vaccination programmes over a period-of two to three years will greatly reduce the incidence of clinical disease [6][11].

Animals that recover from infection with any strain of capripoxvirus, whether of bovine, ovine or caprine origin, are resistant to infection with any other capripoxvirus strain. It is therefore possible to protect cattle against LSD using strains of capripoxvirus derived from sheep or goats [7][11], although the level of protection is not the same, as described later in this document.

Two live attenuated strains of capripoxvirus are the most widely used as vaccines for the control of LSD: a Kenyan strain of Sheep Pox virus (KSGP or KS-1) and a cattle strain of LSDV (Neethling type) from South Africa [5][15]. Vaccination is believed to trigger lifelong protection. Both strains of capripoxvirus used as vaccines can produce large local reactions at the site of inoculation in *Bos taurus* breeds, which discourages the use of the vaccine and increases the size of the susceptible population [5]. Other capripox vaccine strains have also been developed.

Disease situation and government policies by country

Tables 3 and 4 below have been completed with the information received so far from the questionnaires sent to the DG and DVS.

Table 3 covers the disease situation (if it is notifiable or not), the presence of official surveillance and/or control programs, and the treatment situation. Table 4 refers to vaccination.

The definitions that were given to the respondents are:

1Surveillance: is the systematic ongoing collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken.

2Control: a program which is approved, and managed or supervised by the Veterinary Authority of a country for the purpose of controlling a vector, pathogen or disease by specific measures applied throughout that country, or within a zone or compartment of that country.

Table 3: Official status, official programs for LSD in the countries of interest. Information provided by the questionnaire sent to the DG/DVS as part of this monograph.

Country	Notifiable (yes/no)	Official surveillance[1] program (yes/no) If yes, active or passive	Official control[2] program (yes/no)	Treatment (Chemotherapy)	
				Treatment authorised (yes/no)	Frequently practiced (yes/no)
Burkina Faso					
Côte d'Ivoire (Ivory Coast)	Yes	Yes, passive but active if outbreaks	Yes	Yes	If animals are sick
Ethiopia					
Kenya	Yes	Yes, passive	No	No	No
Madagascar					
Malawi	Yes	Yes, passive	No	N/A	N/A
Mali	Yes	Yes, passive	No	No	No
Mozambique					
Rwanda	-	-	-	-	-
Senegal					
South Africa					
Tanzania	Yes	Yes, passive	No	No	No
Uganda	Yes	No	No	Yes (secondary infections)	Yes
Zambia	Yes	Yes, passive	Yes	Yes	No

Table 4: Vaccination for LSD in the countries of interest. Information provided by the questionnaire sent to the DG/DVS as part of this monograph.

Country	Vaccination			
	Compulsory vaccination (yes/no)	Who pays for the vaccine (Government, farmers, combination, others-specify)	Who delivers the vaccine (official, private vaccinators or both)	Species vaccinated (cattle, sheep, goats, pigs, poultry)
Burkina Faso				
Côte d'Ivoire (Ivory Coast)		Farmer	Private	Cattle
Ethiopia				
Kenya	No	Farmer	Both	Cattle
Madagascar				
Malawi	No	Combination of government and farmers	Both	Cattle
Mali	No	Combination	Official	Cattle
Mozambique				
Rwanda	-	-	-	-
Senegal				
South Africa				
Tanzania	No	Farmers, private	Private	Cattle
Uganda	No	Combination	Both	Cattle
Zambia	Yes	Combination	Official	Cattle

Note that Zambia is the only country that has reported compulsory vaccination.

Vaccines Available

Current vaccine types

Only live attenuated vaccines are currently commercially available against LSD. They are generally cheap and provide good protection if sufficient herd immunity (over 80%) is maintained by carrying out annual vaccinations.

Broadly the current live attenuated vaccines used against LSD can be grouped into homologous vaccines (the Neethling and KS-1), and the heterologous, which are SGP strains (Table 5)

Table 5: The different types of vaccines used for LSD and their strains [3]

Disease	Capripox vaccine strain	Major animal targeted	Comments
SGP	Romania (SPV)	Goats & sheep	
	RM-65 (SPV)		Used in cattle at x10 the SG dose
	Mysore (GPV)		
	Gorgan 5GPV)		
	KS-1 /O240 (LSDV)		
LSD	Neethling strain (LSD)	Cattle	
	KS-1/024 (LSD)	Cattle, sheep and goat	Used for SGP and LSD

Two vaccine strains have been widely and successfully used for decades in the prevention of LSD in cattle populations in Africa: the LSD Neethling virus strain virus, and the Kenya sheep and goat pox virus vaccine. There

are however other strains currently in use in other part of affected regions, of which the Yugoslavian RM 65 sheep pox strain and Romanian sheep pox strain are most common [15]. The vaccines commercially available and licensed for LSD are listed in table 7 below.

LSD Neethling strain vaccine

- Developed in South Africa, and used for decades in Southern Africa, the Neethling strain of LSD was passaged 50 times in tissue cultures of lamb kidney cells and then 20 times on the chorio-allantoic membranes of hens' eggs; for production the vaccine virus is now propagated in cell culture [5][6]. Annual vaccination is recommended.
- According to Coetzer [5], approximately 50% of cattle develop a swelling 10 to 20 mm in diameter at the point of inoculation and this may be accompanied by a temporary drop in milk yield in dairy cows. The swelling disappears within a few weeks. Animals younger than six months of age whose dams were either naturally infected or immunized should not be vaccinated, in order to prevent interference from maternal antibody. However, calves born to susceptible cows are themselves very susceptible and should be vaccinated as soon as possible in the face of an outbreak.
- Besides OBP and MSD (actually produced by Design Biologics) in South Africa, the Neethling strain-based LSD vaccine is currently also produced by NVI in Ethiopia. A modified strain is also produced by Deltamune in South Africa.

Kenyan sheep and goat pox (KSGP)

- Also referred to as Kenyan O240 strain or KS-1 strain.
- Developed in Kenya the KS-1 was passaged 16 times in pre-pubertal lamb testes or foetal muscle cell cultures [6].
- Although derived from a sheep isolate and passaged in lamb testis and baby hamster kidney (BHK) cells, further genomic studies have shown that the strain had a closer nucleic acid identity to LSDV than to SPV or GPV, suggesting that this sheep-derived capripoxvirus virus is in fact a strain of LSDV [4][9].
- As seen with other sheep and Goat pox vaccine when used in cattle for LSD, incomplete protection against LSD has been reported in cattle vaccinated with KSGP [13]. The low level of attenuation for safe use is insufficient for cattle and, in some cases, the vaccine has been observed to still be virulent [7][13].
- The KSGP has never been used or recommended for use in Southern African countries free of SGP, as it was believed to otherwise provide a source of infection for the susceptible sheep and goat populations [5]. Its use as vaccine against LSDV has been restricted to those countries where SPP, GTP and LSD overlap, such as central, Eastern, Western and northern Africa, the Middle East, Turkey, Iraq and Iran.
- The finding that the KSGP is actually an LSD strain should no longer restrict its use for LSD. MCI Santé Animale produce an LSD vaccine (BOVIVAX) based on the KSGP strain, while several African government vaccine manufacturers produce a KSGP vaccine for use against LSD and SGP (Table 6).

The other strains used as LSD vaccine

- The Yugoslavian RM65 SPPV vaccine, at a 10 times higher dose than indicated for sheep, has commonly been used for cattle across the Middle East.
- In Egypt both the Romanian SPP and Kenyan sheep and goat pox (KSGP) virus vaccines have been used for cattle [6][13].
- The Bakirkoy SPV (at three to four times the recommended dose for sheep) has been used in Turkey against LSDV [13].

It is important to note that incomplete protection against LSD has been reported in cattle vaccinated with sheep pox derived vaccines [13].

Neutralizing antibodies to LSDV persist for at least two to three years after vaccination. In some animals, the antibody levels are too low to demonstrate, but they are, nevertheless, still resistant to challenge [5]. Antibodies appear 10 days after vaccination and reach the highest level 30 days post inoculation. Calves born to immunised cows will have passive immunity that persists for about six months [5].

Challenges with current vaccines

There have been different reports on safety and efficacy of the different Capripox vaccines used for protection against LSD. Generally, sheep and goat pox vaccine strains tend to have limited efficacy when used in cattle for LSD, and generally are given at a higher titer [4][7][13].

Recently several reports have been published reporting LSD vaccine failure in Ethiopia. The LSDV Neethling and KSGP O-180 strain vaccines, both produced locally by the National Veterinary Institute (NVI) are used in cattle against LSDV in Ethiopia [2][3][8][13]. In 2008 and 2009 re-infection of vaccinated animals was observed during LSDV epidemics. The highest morbidity (15.1%) and mortality (5.37%) of LSD were observed in vaccinated feedlot cattle rather than in extensively managed cattle [2]. Another study in Ethiopia reported morbidity and mortality rates of 22.9% and 2.31% respectively in fully vaccinated herds [3]. Similar vaccine failure has been reported in sheep vaccinated against SGPV using the NVI KSGP O-180 vaccine [13], highlighting the need for molecular characterization of the vaccine seed viruses and re-assessment of the level of attenuation of the local vaccines.

Recently, Gari et al. [8] compared the efficacy and immunogenicity of NVI LSDV Neethling and KSGP O-180 strain vaccines and the Gorgan GTP strain vaccine (CaprivacTM, Jordan Bio-Industries Center, Amman, Jordan) produced by the Jordan Bio-Industries Centre (JOVAC). The study included vaccine challenge experiments in a controlled environment and monitoring of immune responses in vaccinated animals in the field. The Ethiopian Neethling and KSGP O-180 vaccines failed to provide protection in cattle against LSDV, whereas the Gorgan GTPV vaccine protected all the vaccinated calves from clinical signs of LSD. Moreover, the Gorgan GTPV vaccinated cattle showed higher levels of cellular immune responses at the vaccination site, consistent with greater immunogenicity [8].

It is important to note that there is no indication on whether the poor results seen with the NVI Neethling vaccine are linked to the product quality or to the strain itself. As stated earlier in this section, it will be important, among other things, to conduct further evaluations, including molecular characterization, of the vaccine seed viruses and re-

assessment of the level of attenuation of the local vaccines.

Following the use of the vaccine in Israel during the different outbreaks that occurred a study was conducted by a team of the Koret School of Veterinary Medicine, Hachaklait **(Prof. Eyal Klement)**, where the OBP Neethling vaccine was compared to 10x dose of RM65 strain vaccine from Jovac and ABIC. From the results obtained, it was concluded that the Neethling vaccine had a better relative effectiveness than the RM65 in preventing LSD in cows when full immunity is anticipated, and in preventing severe and confirmed LSD cases. The Neethling strain was able to cause non-severe disease in a proportion of animals, and could also spread to non-vaccinated animals.

Commercial vaccines manufactured in Africa and Asia

Table 6: Lumpy skin disease vaccines manufactured in Africa

Vaccine name	Manufacturer	Hosts	Pathogens vaccinated against
Herbivac LS	Deltamune	Cattle	Lumpy skin disease [Neethling] virus (Attenuated)
LUMPIVAX	Kenya Veterinary Vaccines Institute-KEVEVAPI	Cattle	Lumpy skin disease [Neethling] virus (Attenuated)
Lumpy Skin Disease (LSD) Vaccine	National Veterinary Institute of Ethiopia (NVI)	Cattle	Neethling (Attenuated)
Lumpy Skin Disease Vaccine for Cattle	Onderstepoort Biological Products Ltd.	Cattle	Lumpy skin disease [Neethling] virus (Attenuated)
Lumpyvax	MSD Animal Health [Intervet, Schering- Plough Animal Health, Merck Sharp & Dohme, Coopers Animal Health]	Cattle	Lumpy skin disease [Neethling] virus (SIS type) (Attenuated)
CaprivacTM	Jordan Bio-Industries Centre (JOVAC)	Cattle	Gorgan GTP strain
Tissue Culture Sheep Pox Vaccine	Veterinary Serum and Vaccine Research Institute - Egypt	Cattle	Strain not mentioned

	ABIC Israel	Cattle	Yugoslavia RM65 (10x sheep dose in cattle
NODULOVAX	LANAVET; Garoua, Cameroun	Cattle	KSGP strain; also for SGP
DERMAPOX	LCV Bamako, Mali	Cattle	KSGP strain; also for SGP
CLAVESEC	ISRA Senegal	Cattle	No strain information
BOVIVAX	MCI Santé animale	Cattle	Kenya strain > $10^{4.5}$ TCID50

Commercial vaccines imported into Africa and Asia

The information summarised in Table 7, is based on a questionnaire send to the Director of Veterinary Services office and regulators of the countries of interest. Note that some vaccines might have been imported under DVS dispensation, and they are not necessary licensed in the country.

To the best of our knowledge, none of the target countries, in the exception of South Africa, Zambia and to a limited extend Mozambique, practices vaccination.

Table 7: Vaccine imported into the different countries

Country	Vaccine name	Strain or type	Country of origin	Doses imported 2015	Doses imported 2014	Doses imported 2013	Doses imported 2012
Burkina Faso							
Côte d'Ivoire (Ivory Coast)	-	-	-	-	-	-	-
Ethiopia							
Kenya	-	-	-	-	-	-	-
Madagascar							

Malawi	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mali	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mozambique							
Rwanda	-	-	-	-	-	-	-
Senegal							
South Africa							
Tanzania *	Attenuated LSD		South Africa	30			
Uganda*			Kenya	10,000	24,000	0	20,000
Zambia			South Africa	291,500	110,000	42,100	

* Source: Head of the local regulatory agencies

Other comments

JOVAC, the manufacturer from Jordan was also sent a questionnaire designed for key importers into the region. They confirmed that they export LSD vaccine (Jovivac Strong), strain RM-65 to Asia and Africa. They did not specify the countries or the volumes.

Characteristics of Ideal Vaccine Candidates for Smallholders

The recent spread of LSD toward Europe has triggered increased focus on vaccines more suitable for non-endemic areas, preferably non-replicating, DIVA, with increased focus on safety. Enzootic regions however, which represent most of the African continent, need preferably efficacious, affordable and available LSD vaccines. In addition to the availability of such vaccines, these regions need vaccination programs that are implemented and adopted in all livestock communities.

Table 8: Vaccine imported into the different countries

	Attribute	Minimum (current available vaccine)	Ideal
1	Antigen	Immunogen with protective antigens of capripox viruses that protects against LSD infection	Immunogen capable of providing full protection in cattle against LSDV infection
2	Indication for use	For active immunization of cattle & water buffaloes	For active immunization of cattle, water buffalos and all susceptible animals
3	Recommended species	Cattle, Water buffaloes	All LSD and capripox susceptible livestock
4	Recommended dose	2 ml	1 ml
5	Pharmaceutical form	Reconstituted injectable solution/suspension (freeze-dried vaccine) or ready to use solution (inactivated vaccine)	Ready to use solution/suspension
6	Route of administration	intramuscular	SC, Intramuscular or pour on
7	Regimen -	Single dose	Single lifetime dose

	primary vaccination		
8	Regimen - booster	Single annual booster	Lifelong immunity after primary vaccination
9	Epidemiological relevance	Protection against all geographically distinct strains of LSD	Protection against capripoxes and prevention of virus transmission
10	Recommended age at first vaccination	Animals over 3 months: one injection	From 1-2 months of age
11	Onset of immunity	2-3 weeks following primary vaccination	One week following primary vaccination
12	Duration of immunity	At least 1 year	Lifelong immunity
13	Expected efficacy	To prevent disease & prevent mortality.	To prevent infection and transmission. No disease & no mortality in vaccinated animals after virulent challenge.
14	Expected safety	In animals under 6 months of age, a transient pyrexia reaction can occur. A transient nodular reaction of varying importance, may appear at the injection site, it progressively disappears within 1 to 2 months. Only vaccinate pregnant animals on emergency.	No post-vaccinal reactions at any age. Safe for pregnant animals. No carrier form in vaccinated animals
15	Withdrawal period	Nil	Nil
16	Special requirements for animals	Do not vaccinate un-healthy animals	Do not vaccinate un-healthy animals DIVA
17	Special requirements for persons	None	None
18	Package size	50 doses	Multiple pack size from 50 doses
19	Price to end user	Not more than $0.50/dose	$0.20/dose at end user
20	Storage condition and shelf-life as packaged for sale	12 months at 4-8° C	24 months 4-8° C and/or 48 hours at 30° C
21	In-use stability	1 hour	24 hours

Overall conclusion for improved LSD control through vaccination

- The spread of LSD toward Europe is triggering increased interest in the development of more efficacious and safer vaccine that could prevent infection and spread of the wildtype virus, and also have DIVA characteristics. All vaccines available to date have been live attenuated and not always possessing these characteristics.
- The work initiated several years ago in South Africa, CIRAD and PIrbright (UK) for the development of a capripox vector expressing foreign genes, but still being able to immunise against LSD is being boosted, also taking advantage of continuous scientific progress.
- In most endemic countries, where the disease has been causing serious economic losses, the main challenge is the availability of the vaccine and the lack of clear vaccination programs.
- It seems also very critical that good quality vaccines, especially the only homologous currently available, the Neethling strain, be made available and used in highly affected regions. In these regions, a DIVA vaccine may not be a priority

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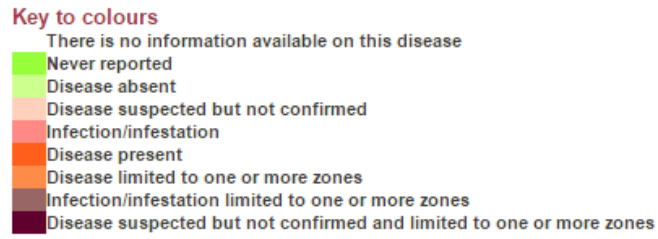
ANNEX 1: Additional data on disease presence and incidence

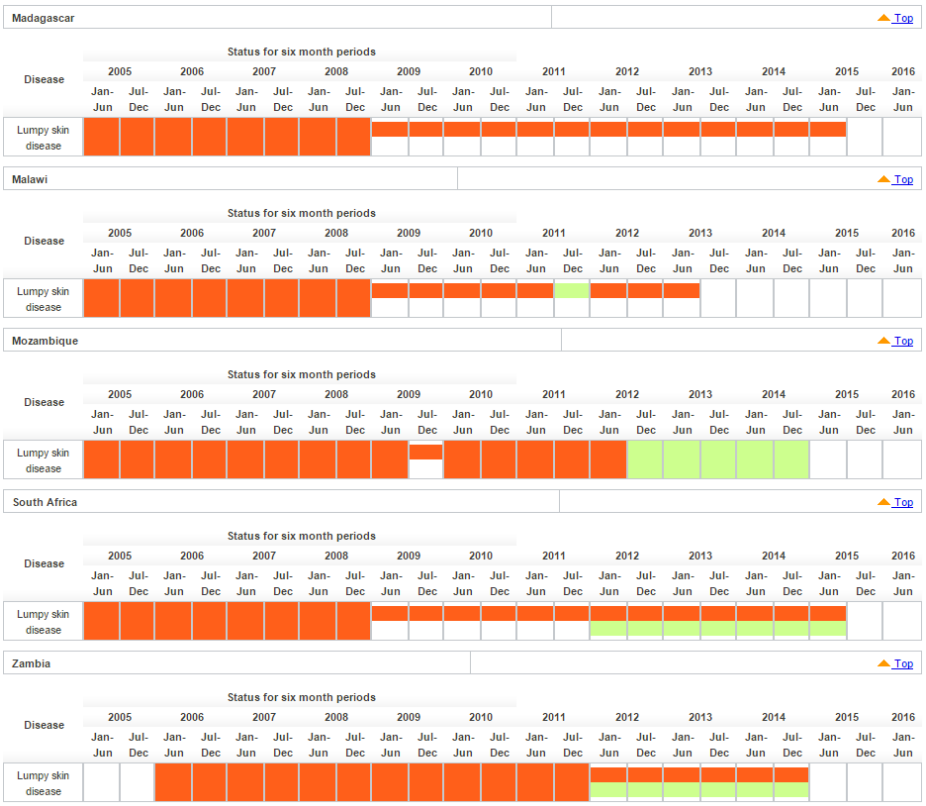
Reports to OIE on LSD:



When different animal health statuses between domestic and wild animal population are provided, the box is split in two: the upper part for domestic animals, and the lower part for wild animals.

LSD in Eastern Africa: Ethiopia, Kenya, Rwanda, Tanzania and Uganda

LSD in Southern Africa: Madagascar, Malawi, Mozambique, South Africa and Zambia



LSD in Western Africa: Burkina Faso, Ivory Coast, Mali and Senegal